

Integrating clinical and genomic factors to predict time to first treatment in chronic lymphocytic leukemia

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OBJECTIVES

The primary objective of the study is to identify the most frequent clinical variables and genetic alterations that influence TTFT, aiming to deepen the understanding of their prognostic value.

CONCLUSIONS

In conclusion, the study successfully identified a set of high-risk genetic mutations – specifically *SF3B1* – that are independently associated with a shorter TTFT. While the established IPS-E prognostic scale does not currently incorporate these identified genetic alterations, the findings from this study strongly suggest the potential utility of developing predictive models that integrate genetic information alongside traditional clinical factors for more accurate risk stratification. However, to robustly validate this proposal and confirm these results in broader populations, larger studies with a greater sample size will be necessary.



INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in adults, marked by significant clinical heterogeneity. Most patients are diagnosed in early, asymptomatic stages, where the standard approach is active surveillance until disease progression warrants treatment. In this context, time to first treatment (TTFT) is a key parameter for assessing disease evolution.

Various clinical and biological factors have been previously identified and associated with a shorter TTFT. These factors include components of the IPS-E prognostic scale, such as lymphocytosis, the presence of adenopathy's, and the *IGHV* mutational status. Other established risk factors are elevated beta-2 microglobulin levels, advanced disease stages according to the Rai classification I-IV and Binet classification B-C, and age over 65 years. Furthermore, the advent of Next-Generation Sequencing (NGS) has facilitated the identification of specific genetic alterations with established prognostic value. Studies, including those proposed by Mansouri *et al.* (*Leukemia*, 2023) (1), have correlated these genetic alterations with a decrease in TTFT.

METHODS

The study was designed as a multicenter, retrospective, and observational analysis. It involved the analysis of clinical and genomic data from patients diagnosed with CLL between 2009 and 2023. The data were collected from two hospitals in Spain: Hospital Universitario de Gran Canaria Dr. Negrín and Hospital Universitario de Canarias (Tenerife). Inclusion criteria stipulated that all patients included must not have required initial treatment at the time of diagnosis, adhering strictly to the criteria defined by the International Workshop on Chronic Lymphocytic Leukemia (iwgCLL).

Genetic testing was performed at diagnosis using NGS with the SOPHiA Genetics v3 panel for CLL, restricted to pathogenic or likely pathogenic variants with a Variant Allele Frequency (VAF) ≥10%. Mean sequencing coverage was 4495x. Statistical analysis included univariate chi-square tests and multivariate Cox regression. Variables with $p \leq 0.25$ in univariate analysis were included in the multivariate models. Survival curves were generated using Kaplan-Meier and compared with the Log-rank test.

RESULTS

The study analyzed 70 CLL patients, of whom 8 (11.4%) required treatment during follow-up. As shown in table 1, the cohort was predominantly male (62.9%) and over 65 years old (57%). Frequent clinical features included lymphocytosis $>15 \times 10^9/L$ (31.4%), palpable lymphadenopathy (31.3%), and $\beta 2$ -microglobulin $>2.5 \text{ mg/L}$ (43.1%). The most common genetic alterations were unmutated *IGHV* (28.3%) and trisomy 12 (18.2%), while *TP53* (8.6%), *NOTCH1* (11.4%), and *SF3B1* (10%) mutations appeared less frequently.

Due to sample size limitations, a "high-risk genetic variable" was created for TTFT univariate analysis ($p \leq 0.25$), grouping mutations in *SF3B1*, *ATM*, and *NFKB1E*. Notably, *TP53* mutations did not show a significant association with TTFT in this univariate setting. The survival analysis demonstrated a statistically significant difference in TTFT based on the presence of these high-risk mutations (62 months vs 198 months ($p < 0.001$)) (figure 1).

In the multivariate analysis (table 2), the unmutated *IGHV* status was consistently and significantly associated with a worse prognosis regarding TTFT ($p < 0.05$) and was associated with higher hazard ratios (HR). Furthermore, patients with any mutation in the high-risk genes – and especially *SF3B1* – presented a higher risk of progression. This increased risk was observed independently of *IGHV* status, thereby reinforcing their value as adverse prognostic markers.

The observed absence of association for *TP53*, this finding could potentially be attributed to the limited sample size of the cohort. Additionally, the study methodology only considered mutations in the *TP53* gene and did not include the detection. Furthermore, later studies, such as that by Malcikova *et al.* (*Leukemia* 2024) (2), have suggested that the impact of *TP53* mutations on TTFT might be restricted primarily to cases with mutated *IGHV*.

REFERENCES

- Mansouri *et al.* (*Leukemia*, 2023)
- Malcikova *et al.* (*Leukemia* 2024)

DISCLOSURES

No disclosures

Table 1. Baseline characteristics of the study cohort (p-values for difference from expected proportion [50%]).

VARIABLES	N (%)	Missing values (n)	p-value*
Age >65 years	40 (57)	0	0.282
Male	44 (62.9)	0	0.041
Presence of adenopathies	21 (31.3)	3	0.003
Analysis			
B2M >2.5 mg/L	22 (43.1)	19	0.401
Hemoglobin <12g/dL	4 (6.1)	4	0.000
Platelets <150 x10 ⁹ /L	10 (14.9)	3	0.000
Lymphocytosis >15 x 10 ⁹ /L	22 (31.4)	0	0.003
FISH			
Normal	20 (35.1)	13	0.033
Del(13q)	22 (39.3)	14	0.141
Trisomy 12	10 (18.2)	15	0.000
Del(11q)	3 (4.3)	0	0.000
Del(17p)	1 (1.4)	0	0.000
Unmutated IGHV	17 (28.3)	10	0.001
IPS-E >1	11 (22.9)	0	0.000
NGS			
TP53 mutation	6 (8.6)	0	0.000
SF3B1 mutation	7 (10)	0	0.000
XPO1 mutation	1 (1.4)	0	0.000
NOTCH1 mutation	8 (11.4)	0	0.000
ATM mutation	1 (1.4)	0	0.000
NFKB1E mutation	3 (4.3)	0	0.000
BIRC3 mutation	2 (2.9)	0	0.000

* p-values for difference from expected proportion [50%].

Figure 1. Kaplan-Meier survival analysis of time to first treatment by high-risk mutation status.

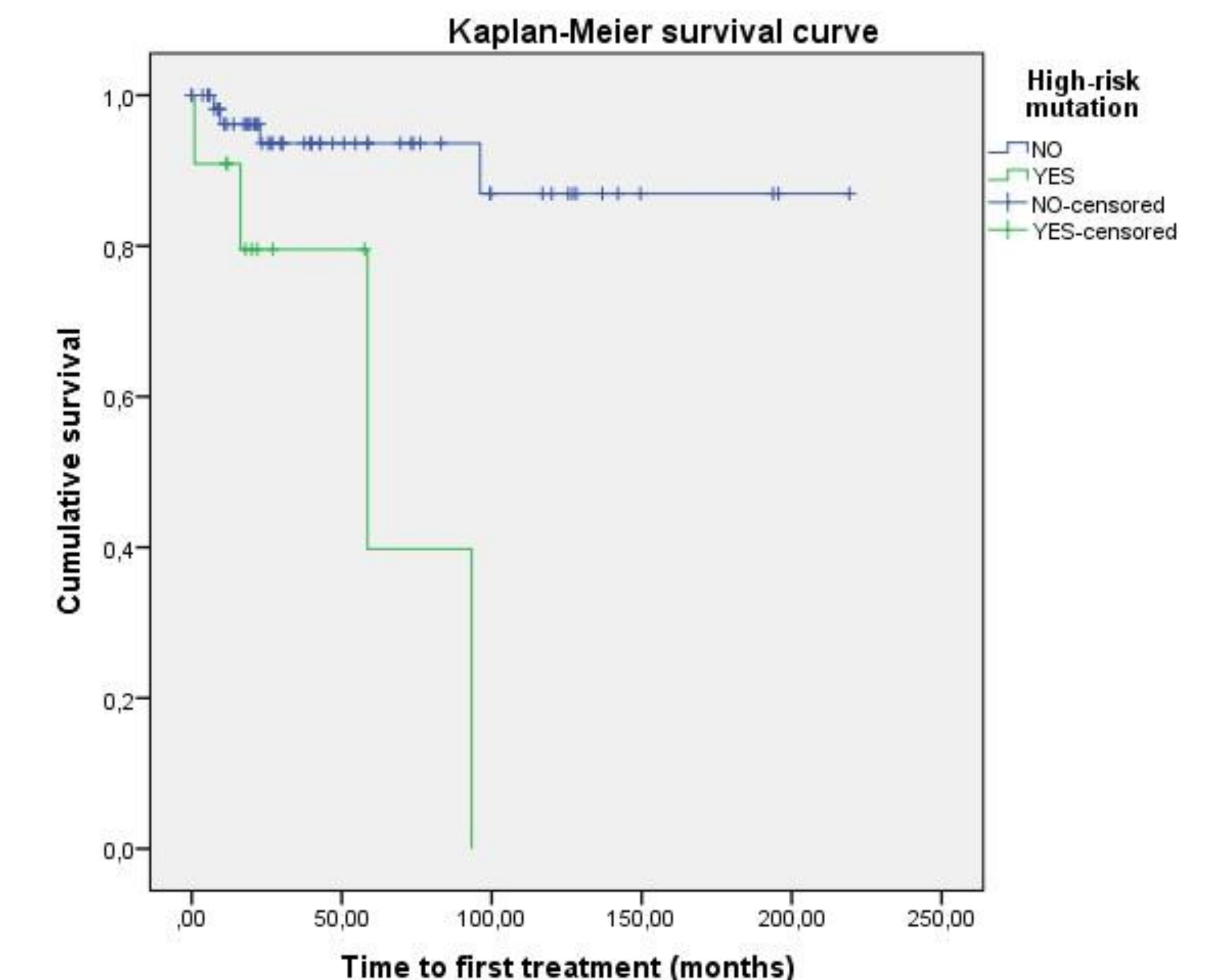


Table 2. Multivariate cox regression analysis of clinical and genetic factors associated with time to first treatment in CLL.

Variables	n	TTFT			
		p-value	HR	95% CI	
Multivariable 1	Age >65 years	70	0,98	0,985	0,20-4,76
	Unmutated IGHV	60	0,004	9,788	2,09-45,68
	Genetic mutation	70	0,004	11,222	2,15-58,58
Multivariable 2	$\beta 2$ -microglobulin	51	0,98	1,016	0,14-7,20
	Unmutated IGHV	60	0,01	22,120	2,96-625,10
	Genetic mutation	70	0,006	43,080	2,05-237,82
Multivariable 3	Age >65 years	70	0,47	1,734	0,37-7,95
	Unmutated IGHV	60	0,002	18,772	2,92-100,30
	SF3B1 mutation	70	0,01	15,19	1,89-122,32
Multivariable 4	$\beta 2$ -microglobulin	51	0,64	1,537	0,25-9,39
	Unmutated IGHV	60	0,03	8,809	1,23-62,88
	SF3B1 mutation	70	0,03	11,697	1,25-108,75